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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/660,384	09/11/2003	Yann Echelard	GTC-32D	6941

31904 7590 10/20/2006

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/660,384	ECHELARD ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92-130* is/are pending in the application.

4a) Of the above claim(s) *105,110 and 116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-115 and 117-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *IDS form from 10/731,542*.

DETAILED ACTION

This application is a divisional of 09/298,508, filed April 22, 1999, now ABN, which claims benefit of 60/106,728, filed November 2, 1998.

Applicants' amendment filed July 28, 2006 has been received and entered. Claims 1-91 have been cancelled. Claim 97 has been amended. Claims 92-130 are pending.

Election/Restrictions

Applicant's election of group I, and the species of primary fibroblasts as a cell type, caprine as a species of animal and anti-thrombin for protein produces in the reply filed on July 28, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that Applicants indicated that upon the determination that the species are allowable, any non-examined species will be rejoined and examined (page 9). As indicated in the restriction requirement, it is upon the allowance of a **generic** claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141(**emphasis added**), not single species. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

With respect to the election of species, upon reconsideration for the sake of compact prosecution, Examiner does not consider the genus of any animal or protein produced to be a burden. Therefore, the election of species for these two are withdrawn.

Claims 92-130 are pending. Claims 105, 110, 116 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 28, 2006. Claim 93-104, 106-109, 111-115 117-130, drawn to a method for producing a transgenic animal comprising performing nuclear transferring methodology twice with a fibroblast cell.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

No IDS has been filed.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless

the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claims 92 and 104 are objected to because of the following informalities:

The claims appear to be incomplete as the final step listed, in that they do not result in the intent set forth in the preamble of the claim, only a final step of nuclear transfer. There is no indication what is practiced after this step or how it produces an acceleration to making a transgenic animal.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 93-104, 107-109, 111-115 117-130 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for cloning a non-primate mammal through a nuclear transfer process using non-primate mammalian cells as a source of donor nuclei comprising an additional recloning step using a cell from a first nuclear transfer embryo, said method wherein it further comprises genetically modifying a fibroblast cell in vitro prior to the initial nuclear transfer, and a non-primate mammal made by the method wherein when the mammal is transgenic and the transgene is expressed, does not reasonably

provide enablement for the claimed method in a primate species, for the claimed method wherein a transgene is introduced into non-fibroblast somatic cells in culture, or for a transgenic non-primate mammal wherein the transgene is not expressed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

The claimed invention is directed to methods for producing a non-human mammal by transferring the nucleus of a differentiated mammalian cell into an enucleated oocyte and simultaneously fusing and activating the resulting cell couplet, culturing the resulting first

embryo until at least the 2-cell stage and using at least one cell from said first embryo as a donor cell for the nuclear transfer to form a second embryo. Dependent claims are drawn to genetic modification of the donor nucleus prior to insertion into an enucleated oocyte. For the purpose of examining the claims under the enablement requirement, the claim is interpreted as reading on a method of cloning a transgenic non-human mammal using a donor cell from a transgenic mammal as well as using a non-transgenic mammal as a source of the differentiated donor cell of step followed by in vitro transformation.

Claims 93-104, 107-109, 111-115 117-130 are broad in that they encompass methods of cloning primate mammals or the resultant offspring or embryo. The specification teaches applying the claimed method to goats, which are non-primate, ungulate mammals. The specification fails to provide any guidance with respect to cloning primates. The primate embodiments of the claims are not enabled because of the art-recognized inability to clone primates. Vogel [**Science**, 300:226-227 (2003)] state that Rhesus monkey nuclear transfer (NT)-generated embryos seemed normal at their early stages but were unable to develop further when implanted into a surrogate mother. This was because the cells had the wrong number of chromosomes, and that this aneuploidy resulted in the abortion of the fetus. This was found to also be the case with human NT embryos. See p. 225. Simerly *et al.* [**Science**, 300:297 (2003)] state that, "Primate NT appears to be challenged by stricter molecular requirements than in other animals ... With current approaches, NT to produce embryonic stem cells in nonhuman primates may prove difficult - and reproductive cloning unachievable." See p. 297, 3rd column, last sentence. As the state of the art evidences, NT in primates is unpredictable, and the instant specification fails to provide teachings to show that primate NT using the claimed methods

would result in pluripotent mammalian cells, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

The claims that require genetic modification, including gene targeting by homologous recombination of the donor nuclear genome prior to insertion of the donor nucleus into the recipient cell. The claims encompass in vitro genetic modification of a cell after isolation from a mammal, just prior to insertion into the oocyte recipient. Similarly, the claims if interpreted as being drawn to a method of cloning a non-human mammal that results in formation of a transgenic embryo using a non-transgenic donor cell also reads on genetic modification of a somatic donor cell *in vitro* Thus, the claims to the extent that they encompass non-enabled embodiments requiring introduction of a transgene into a differentiated, non-fibroblast somatic cell *in vitro*, prior to introduction of said cell of nucleus into an enucleated oocyte. The specification teaches making transgenic goats using the claimed methods by using fetal fibroblast cells derived from an established transgenic CFF6 line of goats as nuclear donors. The specification does not teach in vitro transformation of fetal or adult somatic cells immediately prior to nuclear transfer as encompassed by the claims. The art at the time of filing held that genetic modification of somatic cells in culture was an underdeveloped art.

At the time of filing, the only somatic cell type that could be genetically modified in culture to form an animal was a fibroblast [Schnieke et al. 1997, **Science**, 278:2130-2133]. Thomson et al. [**Reprod. Supp.**, 61:495-508, 2003] review the state of the art of gene targeting in somatic cells for use in nuclear transfer methodologies and state that procedures to enhance the lifespan of targeted somatic cells in vitro are needed. In particular, Thomson states that premature senescence often occurs, which makes it difficult to confirm a targeting event in

somatic cells and that cloning efficiency has been negatively correlated with passage number. See p. 501. The inefficiency and unpredictability of homologous recombination in somatic cells is supported by Polejaeva and Campbell [**Theriogenology**, 53:117-126, 2000] who teach that gene targeting in somatic cells is unpredictable because of the lower frequency of homologous recombination than ES cells, and a finite capacity for number of cell divisions. Polejaeva and Campbell further discuss specific criteria for more efficient somatic cell gene targeting, such as the ability of the cells to have a high single cell-cell cloning efficiency because during drug selection, the cells must be able to expand into clonal cultures. However, they note that human dermal fibroblasts are not able to proliferate under regular culture conditions, and thus, optimization of culture conditions must be attained for success in somatic cell gene targeting. See p. 120-121. Denning taught that primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence [**Cloning and Stem Cells**, 3:221-231, 2001, specifically refer to page 222, col. 1, lines 5-8]. In a study of sheep and goat primary somatic cells, Denning found that of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. Sheep primary cell cultures primarily were composed of fibroblasts after the third passage or about 12 doublings (Denning, page 224, col. 2, lines 11-13). In a similar analysis of pig primary cultures, fibroblasts, as in the sheep study, became the predominant cell-type after three passages, but, unlike sheep, pig fibroblasts underwent a crisis after 40 population doublings and had an unstable karyotype (Denning, page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). Additional studies of cell cultures prepared from fetal pig organs (gut, kidney, lung and mesonephros) showed that these

cells senesced or entered crisis after even fewer doublings than the fibroblast cultures (page 225, col. 1-2, bridg. sent.). The art further taught at the time of filing, that the even if sufficient population doublings could be achieved for selection, many of the pure sheep targeted clones senesced before they could be expanded for nuclear transfer, meaning that targeting frequency was lower than expected (page 228, col. 1-2, bridg. sent.). Similar experiments in pigs demonstrated that all the clones senesced, and no targeted cells for nuclear transfer were obtained. Clearly, the art supports the unpredictability and underdeveloped nature of gene targeting using any somatic cell type for use in nuclear transfer methodologies, and more specifically, that candidate somatic cells that would be used for gene targeting must be able to survive multiple rounds of cell division, selection and overcome senescence. The specification fails to provide teachings or guidance for utilizing any somatic cell for gene targeting which would be further used in nuclear transfer methods. While the state of the art supports that particular cell types, such as fetal fibroblasts, can be used in the claimed methods, specific guidance must be provided to enable the breadth of the claims.

Clearly, the art has established unpredictability in the gene-targeting and random introduction of transgenes to any somatic cell type for use in nuclear transfer methodologies, and has acknowledged that candidate somatic cells that would be used for recombinant DNA technology must be able to survive multiple rounds of cell division, selection and overcome senescence. Therefore, in addition to the aspects set forth above, with respect to the aspect of the claimed invention involving genetic modification of a donor cell in vitro, the specification is further not enabling for making a transgenic nuclear transfer mammal by any means other than use of a fetal fibroblast cell.

To the extent that the claims read on a transgenic non-human mammal, claim 20 does not require expression of the transgene. The specification teaches cloning a transgenic goat expressing a desired protein in the milk as a means of producing large quantities of the protein. The specification does not teach how one of skill in the art would use a transgenic non-human mammal that does not express the transgene. It would require undue experimentation to determine how to use the claimed transgenic mammals wherein the transgene is not expressed. The specification teaches cloning a transgenic goat expressing a desired protein in the milk as a means of producing large quantities of the protein. The specification does not teach how one of skill in the art would use a transgenic non-human mammal that does not express the transgene. It would require undue experimentation to determine how to use the claimed transgenic mammals wherein the transgene is not expressed.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 130 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the term "primary derived fibroblasts" is vague and unclear. Unlike a cell line or primary cell, the term is not art accepted and it is unclear what this cell represents, or how it is differentiated from either a cell line or a primary cell in culture.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 93-104, 106-109, 111-115 117-130 are rejected under 35 U.S.C. 103(a) as being obvious over Schnieke et al. (1997, Science, 278:2130-3), Wilmut (1997), Campbell (1996), Campbell [1994, Biology of Reproduction, 50:1385-1393], in view of Zakhartchenko (1999) and Wells (1999).

The claims are drawn to a method of cloning a non-human mammal comprising transferring the nucleus of a differentiated mammalian cell into an enucleated oocyte of the same species, simultaneously activating the resulting cell couplet, culturing the embryo until it reaches at least the two-cell stage and using a cell from said embryo to form a second embryo through a second round of nuclear transfer.

Schnieke taught cloning of ovine, an ungulate, by nuclear transfer using quiescent fetal fibroblasts, which are differentiated, mesodermally derived cells, (page 2130, col. 3, paragraph 4). Schnieke transformed the fibroblasts with a transgene. Schneike obtained oocytes from the same species, sheep, incubated them in medium containing cytochalasinB prior to enucleation (taught by reference at Schnieke page 2131, col. 3, paragraph 3 to Campbell, 1994, page 1386, col. 1, paragraph 5 through Campbell, 1996). Donor cells were transferred into the oocyte and fusion and activation were simultaneously induced by electrical shock pulses (taught by reference at page 2131, col. 3, paragraph 3 and Wilmut, page 813, col. 1, paragraph 3). It is noted that Schnieke taught many of the claim limitations by reference to which can be found at page 813 of Wilmut and also, by further reference to Campbell, 1996 that references Campbell, 1994. It is also noted that the oocytes were recovered at metaphase II from the oviducts (see Campbell, 1994, page 1386, col. 1), which are in vivo matured (claim 13). Schnieke did not teach a re-cloning step as required by step (vii) of claim 1.

However, both Zakhartchenko (1999) and Wells (1999) taught growing a first nuclear transfer embryo and using morulae from the first cloning round (see paragraph bridging pages 326-327 of Zakhartchenko and page 998, col. 2, paragraph 4 of Wells). Both Zakhartchenko and Wells each taught increased developmental capacity and cloning efficiency using a recloning step (see Zakhartchenko, page 326, col. 1, paragraph 2 and page 330, col. 1, paragraph 4; see also Wells, page 999, col. 2, paragraph 5).

It would have been obvious for one of skill in the art at the time of filing to combine the teachings of nuclear transfer in cloning a non-human mammal of Schnieke with those of wither Zakhartchenko or Wells, adding a recloning step. One would have been motivated to add a

recloning step because both Zakhartchenko and Wells taught that greater efficiency of cloning resulting in live birth occurs when a recloning step is used. One would have a reasonable expectation of success in combining the above teachings because the techniques necessary for the recloning step were known and are merely repetition of the steps taught by Schnieke.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

2) Claims 93-104, 106-109, 111-115 117-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997) as evidenced by Wilmut (1997), by Campbell (1996) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999) as applied to claims 1,2,5-9,11,13,17,19, 20 and 22 above, and further in view of Campbell (WO 00/42174, published 20 July 2000).

As set forth above, Schnieke taught a method of cloning a sheep using fetal fibroblast cells, however Schnieke did not teach using a wide range of adult cells such as those representing ectodermally or endodermally derived cells, or the cells from any of the specific organs listed in in the claims as a nuclear donor.

However, at the time of filing Campbell taught using any cell population from any stage in the life of an animal (see page 3, lines 25-29, and page 10, line 20-page 11, line 6). Campbell also taught that oocytes could be matured in vitro (page 13, lines 20-22). Furthermore, Campbell taught applying the methods of cloning to ungulate as well as rodent species (paragraph bridging page 3-4).

It would have been obvious at the time of filing to combine the methods of Schnieke and of Zakhartchenko or Wells with the teachings of Campbell using cells derived from an adult mammal to make a cloned mammal by nuclear transfer, including rodent species using in vitro matured oocytes. One of skill in the art at the time of filing would have been motivated to use a cell derived from an adult mammal to avoid having to generate a fetus as well as to clone an adult, rather than cloning a fetal offspring of a desired adult. Use of a somatic cell to clone an adult would allow for formation of genetically identical tissues that could be use to treat diseases, disorder or injury in a mammal. One of skill in the art would have been motivated to use the claimed methods in rodent species because the method provides a means of introducing transgenes into rodent species that are otherwise not amenable to transgenesis. One of skill in the art would have been motivated to substitute in vitro matured oocytes for in vivo matured oocytes because in vitro maturation would allow for harvesting of large numbers of immature oocytes from an ovary of a pig over hormonally inducing in vivo maturation and release of oocytes from pigs in vivo. In vitro maturation also allows for collection of oocytes post-mortem. To the extent that the claims read on cloning a transgenic mammal, as opposed to introducing a transgene into donor cells in culture, one would have a reasonable expectation of success in combining the methods of Schnieke with those of Campbell in using adult cells as nuclear donors because both adult and fetal cells are differentiated, somatic cells. Furthermore, at the time of filing, it was becoming more routine in the art to use adult cells as taught by Campbell and to perform nuclear transfer in both livestock and rodent mammalian species.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach